GLUCOSE METABOLISM AND HORMONE TREATMENT IN CANCER CACHEXIA

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INTRODUCTION

THE TUMOR-BEARING STATE is associated with a decreased insulin glucagon ratio[1] and an increase in the activity of hepatic gluconeogenic enzymes.[2] To reverse these catabolic effects of the tumor, we have used combination hormone therapy with the somatostatin (SMS) analogue, octreotide (which inhibits pancreatic glucagon and insulin secretion) and the anabolic effect of exogenous insulin supplementation. The purpose of this study is to determine the effect of SMS plus insulin treatment on tumor and host growth, the insulin/glucagon ratio, and hepatic gluconeogenic enzyme activity in a rat model of cancer cachexia.

MATERIALS AND METHODS

Female Lewis rats (n = 72) with subcutaneous mammary carcinoma implants (MAC-33) were randomized to receive SMS (150μg/kg intraperitoneal injection twice a day), insulin (2.5 U/kg subcutaneous injection twice a day), combined SMS plus insulin, or saline (placebo) from day 30 to 35 following tumor inoculation. Eighteen nontumor bearing rats receiving saline were used as controls. Host weight and tumor volume were monitored, and at death serum was collected for insulin and glucagon levels by radioimmunoassay. Liver cytosol was assayed for fructose-1,5-diphosphatase (FDP) by an enzymatic reaction measuring NADPH production at 37°C, pH 7.5, over five minutes and lactate dehydrogenase activity (LDH) by the reduction of pyruvate to lactate at 25°C over 20 minutes. Liver microsomes were assayed for glucose-6-phosphatase activity by measuring inorganic phosphate release from glucose-6-phosphate at 37°C over 30 minutes at varying substrate concentrations to determine Vmax by the Michaelis-Menten equation. Statistical analysis was performed by one-way analysis of variance.

RESULTS

The tumor-bearing state is associated with a decreased insulin/glucagon ratio and reduced carcass weight consistent with this catabolic hormone

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*Results of glucose metabolism and hormone treatment on cancer cachexia**

Treatment Group	Insulin/ Glucagon Ratio	Carcass Weight Loss, g	Tumor Weight Gain, g	FDP Activity, Δabs/min/mg	LDH Activity, IU/mg protein	G-6-P Vmax, μMP/min/mg protein
No tumor	4.90 ± 1.3[a]	0.3 ± 1.6[a]	-----	.048 ± .003[a]	3528 ± 136[a]	.252 ± .04
Saline	1.82 ± 0.5[abc]	17.8 ± 3.0[bc]	24.7 ± 2.9[c]	.078 ± .008[abc]	5125 ± 105[abc]	.259 ± .04
Somatostatin (SMS)	4.10 ± 1.0	20.1 ± 2.0	24.3 ± 2.2	.089 ± .007[b]	4792 ± 198	.301 ± .03
Insulin (Ins)	25.0 ± 8.2[b]	16.3 ± 1.5	23.0 ± 1.5	.079 ± .006	5468 ± 289	.313 ± .04
SMS + Ins	113.70 ± 13[c]	4.9 ± 3.5[c]	13.2 ± 1.9[c]	.102 ± .005[c]	5521 ± 186[c]	.385 ± .08

[abc]: P < .05 by one-way ANOVA.
*FDP indicates fructose-1,5-diphosphatase; LDH, lactate dehydrogenase.

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ratio (Table). Combined therapy with SMS plus insulin reverses this catabolic hormone index, prevents carcass weight loss, and inhibits tumor growth, as compared with controls or those receiving single hormone therapy. The tumor-bearing state is associated with an increase in FDP and LDH activity. Combined hormone therapy did not reverse this abnormality, but significantly increased activity, as compared with placebo controls.

DISCUSSION AND CONCLUSION

The gluconeogenic enzyme activity seems to be dependent on substrate availability rather than direct hormonal influence. Hepatic gluconeogenesis may be increased as a result of the hypoglycemic effect of hormone treatment. Nevertheless, combined SMS plus insulin treatment reverses the catabolic decrease in the insulin/glucagon ratio, increases host weight, and inhibits tumor growth. Combined hormone therapy may be clinically useful in the treatment of cancer cachexia.

REFERENCES

1. Chance WT, Van Lammeren FM, Chen MH, et al: Alteration in plasma levels of insulin and glucagon associated with cancer anorexia. Surg Forum 34:441–443, 1983.

2. Noguchi Y, Vrdelingum NA, Brennan MF: The reversal of increased gluconeogenesis in the tumor-bearing rat by tumor removal and food intake. Surgery 106:423–431, 1989.

DOES GLUTAMINE FACILITATE CHEMOTHERAPY WHILE REDUCING ITS TOXICITY?

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IN 1988, FOX AND COLLEAGUES showed that the morbidity and mortality of methotrexate administered to rats was ameliorated by the enteral administration of glutamine.[1] Subsequently, Klimberg et al demonstrated that glutamine, the principal fuel of rapidly growing tumors, does not stimulate tumor growth.[2] Clinical application of these findings has been inhibited by concern that glutamine would not only "protect" the host, but also the tumor, thereby reducing the chemotherapeutic effectiveness

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